Epitomes

Important Advances in Clinical Medicine

Pediatrics

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The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association, and the summaries were prepared under the direction of Myles B. Abbott, MD, Richard L. Oken, MD, and Moses Grossman, MD, and the panel.

Bacterial Resistance and the Dilemma of Antibiotic Usage

IN THE SIXTY YEARS since the first clinical use of sulfonamides, there has been a remarkable explosion of antimicrobial agents. Physicians typically greet the introduction of new agents with enthusiasm, reflected by rapidly increasing use. Predictably, pathogens adapt to the high usage by developing resistance, and the drug's value is severely jeopardized. This pattern of discovery, exuberant use, and predictable obsolescence has occurred with virtually every antimicrobial agent. The pharmaceutical industry has, until recently, dealt successfully with antimicrobial-resistant strains by developing new drugs or drug combinations, often just in the nick of time. But we are now faced with some bacterial pathogens for which virtually no effective antimicrobial agent exists.

Examples of pathogens' adaptation for resistance abound. *Staphylococcus aureus* isolates, once universally sensitive to penicillin, are now invariably resistant to penicillin and sometimes to methicillin and the other semisynthetic penicillinase-resistant penicillins as well. Isolates of *Streptococcus pneumoniae* are also becoming increasingly resistant to penicillin; nationally about 10–15% of strains are relatively resistant (minimal inhibitory concentration [MIC], ≥0.1–1.0 μg/ml) and about 3% are absolutely resistant (MIC ≥2 μg/ml) to penicillin. Although most species of streptococci remain sensitive to β-lactam antibiotics, enterococci are exceptions. A high proportion of enterococci are resistant to ampicillin and aminoglycosides, and some strains are also resistant to vancomycin. In addition, gram-negative pathogens are frequently resistant to antibiotics; as a result of β-lactamase production, 30–40% of strains of *Haemophilus influenzae* and almost all *Moraxella* species are resistant to β-lactam agents. Gram-negative enteric organisms, especially those responsible for nosocomial infections, have developed stepwise resistance to an increasing number of antimicrobial agents. The mechanisms of resistance depend on the type of bacteria and class of antibiotics; for example, β-lactamase production is the principal mechanism of bacterial resistance to β-lactam antibiotics, whereas enzymatic inactivation is the principal mechanism of aminoglycoside resistance among gram-negative pathogens. In the case of *Streptococcus pneumoniae*, the mechanism of resistance is the reduced capacity of penicillin-binding proteins in the bacteria to bind to the antibiotic molecules.

These trends in antimicrobial resistance have substantial implications for the empiric therapy of most bacterial infections. In the ambulatory setting, the most important decision regarding antibiotics is whether they should be used at all. In the first place, it behooves physicians to withhold antibiotic therapy when the most likely diagnosis is a viral infection. If antibiotics are prescribed, an appropriate narrow-spectrum drug should be selected. Physicians should be reluctant to prescribe the latest, broadest-spectrum agent, since this practice will aggravate the problem of increasing drug resistance. Antibiotics also should be prescribed for as short a period of time as possible. For example, the duration of therapy for otitis media, the most common bacterial infection in children, usually can be limited to 5 days (rather than the usual 7–10 days) if the child responds rapidly and is not at high risk for a complicated infection, such as those with frequently recurrent episodes.

For the sick, hospitalized patient who may have a life-threatening bacterial infection, one must carefully consider prevalent patterns of drug resistance before instituting therapy. For example, in most areas of the United States it is no longer acceptable to treat patients with suspected bacterial meningitis solely with penicillin or a third-generation cephalosporin. Increasing resistance of *Streptococcus pneumoniae* (the most common cause of bacterial meningitis in

infants and children) to penicillin and cephalosporins mandates the empiric use of vancomycin, pending definitive identification and sensitivity testing of the bacterial isolate. Physicians caring for hospitalized patients, in addition to carefully selecting antibiotics for the empiric therapy of critically ill patients, must limit the use of broad-spectrum antibiotics that perpetuate multiple drug resistance and predispose these patients to superinfections.

The increase of antimicrobial resistance demands the attention of all physicians. Antibiotics must be used judiciously: the overzealous use of antibiotics in the past has resulted in our compromised ability to manage bacterial infections today. It is only through the thoughtful prescription of antibiotics that the balance between antibiotic use and drug resistance can be regained. Our obligation extends beyond our individual patients to the entire community of patients for whom we are responsible.

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Advances in the Treatment of Respiratory Failure in Newborns

ENORMOUS STRIDES in the treatment of respiratory failure have significantly reduced neonatal mortality and morbidity. Recent advances in technology that target specific respiratory disease processes have further improved the outlook for newborns with respiratory failure.

Hyaline membrane disease (HMD), a major cause of mortality and morbidity in premature infants, is caused by a surfactant deficiency. Extensive animal studies and clinical trials have shown that surfactant replacement is effective in both preventing HMD ("prophylactic" treatment) and treating established HMD ("rescue" treatment). Two forms of replacement surfactant are available for clinical use: Survanta, a modified bovine surfactant, and Exosurf, a totally synthetic surfactant. Infasurf, another modified calf lung surfactant extract, will likely be approved by the FDA soon. In addition to its role in the treatment of infants with HMD, surfactant may be useful for the treatment of other diseases characterized by surfactant deficiency or inactivation, such as meconium aspiration syndrome.

Improved ventilator technology has played an important role in managing neonatal respiratory failure. Intermittent mandatory ventilation (IMV) was the standard mode of therapy for treatment of HMD for more than 30 years. With IMV, a fixed number of breaths is delivered at defined intervals, and the patient has no control over the timing of the breaths. Today, patient-triggered ventilation and high frequency ventilation (HFV) have largely replaced IMV. Synchronized intermittent mandatory ventilation (SIMV) and assist/control ventilation (ACV) allow the patient to adjust the timing of breaths by "triggering" the ventilator. Both SIMV and ACV deliver more uniform breaths than does IMV, and they cause less ventilator-induced variation in arterial blood pressure. SIMV gives a fixed number of breaths each minute, but the breaths are synchronized with the patient's respiratory effort. With ACV, each patient effort is assisted by the ventilator. Clinical trials of both SIMV and ACV suggest that infants ventilated with these patient-triggered modes are extubated sooner than infants ventilated with IMV.

High frequency ventilation (HFV) is principally used in managing critically ill neonates with severe restrictive lung disease, such as respiratory distress syndrome, meconium aspiration, and pulmonary hypoplasia. Unlike conventional ventilators that mimic normal tidal breathing, HFV delivers extremely small breaths at rates as high as 900 breaths per minute. Although these "breaths" are often as small as or smaller than dead space volume, they are able to achieve effective gas exchange primarily by causing gas mixing between the upper airway and the alveoli. The three main forms of high frequency ventilation are high frequency oscillatory ventilation (HFOV), high frequency jet ventilation (HFJV), and high frequency flow interruption (HFFI). HFOV uses an oscillating diaphragm that delivers a sinusoidal pressure wave to the patient, usually at rates between 600 and 900 breaths per minute. HFJV injects small, high velocity, "jets" of gas into the airway, usually at 420 breaths per minute, and operates in conjunction with a conventional ventilator, using a triple-lumen endotracheal tube adapter that allows both ventilators to be connected to the patient simultaneously. HFFI "interrupts" the flow of gas to the upper airway, generating high frequency breaths that have some of the characteristics of both HFOV and HFJV breaths. Studies have yielded conflicting results about possible increased neurological morbidities associated with these techniques.

When ventilatory methods fail in term and near-term infants, extracorporeal membrane oxygenation (ECMO) is the next line of therapy. ECMO is a form of prolonged cardiopulmonary bypass, allowing support of infants with severe pulmonary failure. There are two types: venous to arterial and venous to venous. The use of ECMO at designated centers—most commonly for newborns with severe meconium aspiration, pulmonary hypertension, or diaphragmatic hernia—has dramatically reduced the mortality of these disorders. The average responder requires less than a week of ECMO therapy and then is returned to ventilatory support. One major complication from ECMO is intracranial hemorrhage secondary to anticoagulation therapy. A second major complication is the loss of the carotid artery when venous-to-arterial ECMO is used and